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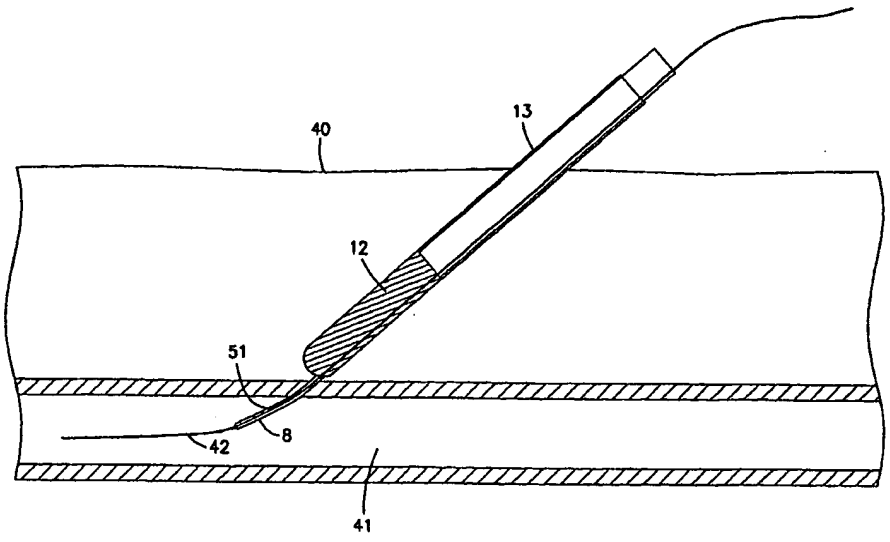

(57) Abstract

The present invention includes a device for achieving hemostasis as part of an intravascular procedure. In one preferred embodiment the vessel is accessed, and a hemostatic composition is infused into the vessel puncture site. In other preferred embodiments, a hemostatic plug (12) is placed against the blood vessel wall (41) at the site of the puncture. Other preferred embodiments are methods of achieving hemostasis as part of an intravascular procedure with the use of hemostatic compositions, and plugs. The present invention includes the use of alginate compositions as hemostatic compositions, and plugs as part of intravascular procedures or other medical procedures.

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DEVICE AND TECHNIQUE FOR PERCUTANEOUS CLOSURE OF VASCULAR PUNCTURE SITES

The present application claims priority from U.S. Patent Applications Nos. 60/111,438, 60/121,371, 60/129.959, and 60/143,251, which are all hereby incorporated by reference in their entirety.

Field of the Invention

The present invention applies to techniques for achieving hemostasis after percutaneous arterial puncture for any purpose, including but not limited to diagnostic radiology and cardiology, as well as interventional radiology and interventional cardiology.

Background of the Invention

Certain medical procedures require intravascular access. In procedures such as cardiac catheterization, counterpulsation and angiography, a catheter or other device is inserted into an artery and fed through the vascular tree to the location of interest. Such procedures are performed most commonly by percutaneous methods, and the access site most usually selected is the groin, where the femoral artery is relatively accessible. However, other arterial access sites as well as venous access sites are intended to be encompassed by the scope of the present invention.

Such percutaneous procedures normally are performed by a Seldinger-type technique

consisting essentially of inserting an angiographic needle into the artery, followed by inserting a guide wire through that needle into the artery. Thereafter the needle is removed leaving the guide wire in place. Next, a sheath-dilator set is fed over the guide wire into the artery in order to re-establish a vascular access route and to enlarge the opening sufficiently to permit insertion of a catheter or other device. Thereafter, the dilator is removed and the sheath or guide cannula remains in place during the procedure. A catheter or other device then can be inserted through the cannula directly into the lumen of the artery.

After the procedure has been completed the catheter or other device, as well as the sheath, is removed and the wound must be closed. Normally this is achieved by the application of pressure to the skin and underlying tissue located above the vessel puncture site. This is commonly applied by direct digital pressure by a medical professional, by a pressure dressing or through the use of sandbags. With respect to arterial puncture sites, customarily pressure is applied for at least ½ hour, and frequently for much longer periods. During this period the patient must be immobilized, lest movement interfere with the sealing of the puncture site. Due to the amount of pressure required, the duration for which the pressure is required, and the mandatory immobilization, the procedure is uncomfortable and may be painful. Such patients also require the prolonged personal attention of a health-care professional. Finally, puncture sites closed in this manner can reopen unexpectedly a substantial period after wound closure apparently has been achieved, therefore patients often are required to remain under close observation for prolonged time periods, which can necessitate a hospitalization.

In an attempt to minimize such problems, physicians performing such procedures can utilize the smallest caliber devices, often however a larger caliber device may be preferable for many of these procedures. There is a need for an effective and simple means of achieving reliable vessel puncture site closure under these circumstance.

A series of devices have been developed in an attempt tc address these problems. Such devices attempt to achieve hemostasis through the application of a variety of means once the procedure has been completed. Examples include those devices described in U.S. Pat. Nos. 4,744,364, 4,852,568 and 4,890,612 to Kensey. These three patents describe a mushroom or umbrella shaped device which is used to seal the artery from the inside. The head of the device is placed within the arterial lumen and means are provided to pull and hold the underside of the head against the inside wall of the lumen. It is believed, however, that sealing from the inside can be the source of its own problems, including the promotion of clot formation inside the vessel. Another method for sealing a puncture wound after removal of a catheter is described in U.S. Pat. No. 4,929,246 to Sinofsky. The approach taken there is to insert a balloon-tipped catheter into the tissue wound, inflate the balloon against the hole in the artery and then use a laser to thermally weld the wound closed. Other approaches include applying hemostatic material around the puncture site after completion of the procedure as described in U.S. Pat, No. 5,437,631. U.S. Patent No. 5,478,352 to Fowler, describes a device and method for closing a puncture by inserting a plug into the wound. This is performed after the procedure is completed and the correct placement of the plug is achieved with the use of a balloon catheter or cylindrical insertion device. U.S. Patent No. 5,437,631 to Janzen describes a device for inserting collagen or other hemostatic materials into a puncture wound after a

blood vessel has been accessed and the puncture site enlarged by the insertion of a vascular stent or dilator. U.S. Patent No. 5,725,498 to Janzen describes the placement of hemostatic material against a punctured vessel wall after a procedure has been completed and requires compression of the blood vessel as a part of the placement of the hemostatic material. U.S. Patents Nos. 5,383,896 and 5,868,778 to Gershony et al. describe devices and methods to effect closure of a blood vessel puncture site after completion of a procedure requiring the insertion of an inflatable balloon device into the lumen of the blood vessel. U.S. Patents Nos. 4,838,280 and 5,080,655 to Haaga describe medical biopsy needles with bioabsorbable gelatin tips and U.S. Patent No. 4,936,835 to Haaga describes a medical needle with a bioabsorbable gelatin tip which can be deposited at biopsy or puncture sites and assist in achieving hemostasis during a biopsy or venosection procedure. U.S. Patent No. 5,443,481 to Lee describes a method of obtaining hemostasis after an intravascular procedure by applying a hemostatic material to the area of the puncture site after the removal of the access device used during the procedure. U.S. Patent No. 5,292,332 to Lee describes a device for sealing a blood vessel puncture site by the insertion of a hemostatic plug into the vessel puncture site. The present invention is believed to overcome most of the disadvantages of the previous methods which require enlarging the blood vessel puncture site, removal of the access device or both before any hemostatic material is placed..

Numerous materials and methods have been proposed for closure of arteries or other blood vessels accessed during catheterization procedures. These various materials and techniques include sutures, staples, cautery, plugs constructed of collagen, gelfoam, and other biomaterials, slurries of microfibrillar collagen combined with procoagulants such as

thrombin, and fibrin glue. The ideal material would be thrombogenic, nonimmunogenic, and bioresorbable, self-adhesive, radiopaque and would be of an appropriate viscosity to allow precise placement outside the vessel wall with relatively little chance of inadvertent placement of the material into the vessel lumen. For some devices, the use of a liquid, slurry, gel, paste, or foam would be preferred over a solid material, since relatively more volume of the former substances can be placed compared to the latter substance in low profile delivery systems. The present invention addresses many of the problems with existing materials and methods.

Summary of the Invention

The present invention comprises a vascular access device with a needle with an access lumen, with which to obtain vascular access, at least one additional lumen for the infusion of a hemostatic composition, and a means of infusing the composition at the site of vascular access, in order to achieve hemostasis as part of an intravascular procedure. One embodiment of the invention contains two or more infusion lumens, for the infusion of different components of the hemostatic composition. The device is for use in any blood vessel that would normally be used for such procedures, including arteries and veins. The infusion lumen or lumens and the access lumen are arranged concentrically, or optionally in a parallel manner adjacent to one another. In a concentric arrangement the infusion lumen or lumens are arranged around the access lumen. In one preferred embodiment the infusion lumens terminate in a mixing chamber, which optionally includes a mesh or a series of baffles to permit more homogeneity via mixing of the components of the hemostatic composition.

The present invention includes a method of achieving hemostasis during an intravascular procedure. The vascular access device of the present invention is inserted into a blood vessel and advanced until the tip and opening of the access lumen is in the blood vessel but the opening(s) of the infusion lumen(s) are adjacent to the exterior of the vessel wall. Thereafter, the hemostatic composition is infused around the vascular puncture site, flow of the composition into the vessel being prevented by the presence of the needle in the puncture site. After the hemostatic composition is infused the vascular procedure is carried out in the usual manner.

One embodiment of the invention comprises a vascular access device with a hemostatic plug which is compressed and constrained by a deployment sheath, which is removable by retraction or by being peeled away once the hemostatic plug is in the desired location. The invention includes a method of using the vascular access device to achieve hemostasis during an intravascular procedure. The access device is inserted and advanced until the tip of the access lumen is in the lumen of the blood vessel. The access device is further advanced until the hemostatic plug abuts the vessel wall and the deployment sheath is then removed, allowing the plug to expand. The device then is removed, being replaced with the usual type of device used for such intravascular procedures. The deployment sheath is of a retractable or peel away design. In another embodiment, the device comprises a hemostatic plug and deployment sheath as well as a lumen through which a guidewire can be fed. The blood vessel is punctured and a guidewire inserted. Thereafter, the guidewire is inserted into the lumen and the device is advanced over the guidewire until the plug is positioned against the vessel wall. The deployment sheath is removed and the plug is permitted to expand.

Optionally, the device includes a channel or lumen through which extravasated blood can flow when the plug is appropriately positioned against the vessel wall. Optionally, the hemostatic plug of the present invention includes a removal filament for the removal of a maldeployed plug.

The hemostatic compositions and plug are composed of compounds which can achieve hemostasis, and include but are not limited to fibrin glue/thrombin, calcium alginate/ionic calcium, sodium alginate/ionic calcium, collagen paste, or synthetic materials. One embodiment of the present invention is the use of alginate compound for the purpose of achieving hemostasis during intravascular and other medical procedures. These hemostatic compounds contain a cationic salt, preferably calcium chloride, guluronic acid and/or mannuronic acid and a liquid or other medium in order to produce a compound which is a solid, a liquid, a gel, or a foam. Optionally the hemostatic composition or plug is rendered radiopaque by the addition of contrast or other radiopaque material.

Brief Description of the Drawings

Other objects and many of the attendant advantages of the present invention will be appreciated by a reading of the detailed description of the invention, especially when considered in conjunction with the accompanying drawings, which are provided for illustration and are not intended to limit the scope of the present invention.

FIG. 1 is a longitudinal cross sectional view of a first preferred embodiment of the invention showing the construction of the infusion lumens but without the access lumen shown.

FIG. 2A is a longitudinal cross sectional view of the first preferred embodiment with a side by side arrangement of the access and infusion lumens

FIG. 2B is a longitudinal cross sectional view of a preferred embodiment with a co-axial arrangement of the infusion and access lumens.

FIG. 2C is a transverse cross-sectional view of the device shown in FIG. 2B along plane 10.

FIG. 3A is a longitudinal cross-sectional view of the distal end of a preferred embodiment with a tri-axial arrangement of the lumens and with a mixing chamber.

FIG. 3B is a transverse section of the portion of the invention shown in FIG. 3A

FIG. 4 is a longitudinal cross-sectional view of a second preferred embodiment of the present invention comprising a hemostatic plug on the access device .

FIG. 5 is a longitudinal cross-sectional view of a preferred embodiment for the deployment of a hemostatic plug after vascular access has been obtained

FIG. 6 is a longitudinal cross sectional view of the distal portion of another preferred embodiment of the invention depicted in FIG. 5

FIGS. 7 A - G show various stages in the application of one preferred method of using the device depicted in Figure 5

FIG. 7A shows a angiography needle inserted in a blood vessel, with a guidewire through the bore of the needle.

FIG. 7B shows the guidewire in place after removal of the angiography needle

FIG. 7C shows the device of FIG. 5 being fed down the guidewire

FIG. 7D shows the hemostatic plug in place against the vessel wall.

FIG. 7E shows the expanded hemostatic plug after withdrawal of the deployment sheath.

FIG. 7F shows the plug in place after removal of the device

FIG. 7G shows the hemostatic plug in place with an angiographic sheath being fed over the guidewire into the vessel after completion of the procedure.

Detailed Description of the Invention

The present invention applies to any technique which is performed using percutaneous vessel (artery or vein) puncture including but not limited to diagnostic and interventional radiology or cardiology. When an artery or vein is punctured, an opening in the vessel wall is created and a catheter or other object is placed in the opening. This is usually but not always performed, using a Seldinger-type technique. Subsequently, the vessel requires closure by some mechanism. Existing devices for vessel closure are placed after insertion of and/or removal of vascular catheters or sheaths, the placement of which result in the creation of large holes within the vessel wall. Additionally, when existing devices are placed the exact location of the vessel wall is not known, because the exact location of the vessel wall is only known at the time of placing the puncture needle through the vessel wall and before the placement, for example, of vascular catheters and sheaths.

One preferred embodiment of the present invention is a device for placing closure materials, including but not limited to either single- or multi-component liquids, gels, or slurries, immediately outside the vessel wall, while greatly reducing the risk of inadvertent placement of the material into the lumen of the vessel. The vascular access device is an

improvement on arterial or venous entry needles, which are used to perform the initial blood vessel puncture. Preferred embodiments of the vascular access device are shown in Figures 2A and 2B. Referring to Figure 2, the device which has a proximal end 30 and a distal end 20, comprises a needle 15, which is a hollow, preferably cylindrical metal device, with a longitudinal bore or access lumen 7 extending from the proximal end 30 to the distal end 20. At the distal end, the needle has a sharp tip 8 for penetration through the vessel wall and entry into the vessel lumen. The present invention has one, additional longitudinally oriented infusion lumen 1, or optionally more than one additional longitudinally oriented infusion lumen 2, which extend from the proximal portion of the device towards the distal end of the device generally parallel to the access lumen, terminating with one, or optionally more than one, opening 4 proximal to the distal opening of the access lumen 8. The distance from the distal opening of the access lumen 8 to the distal opening, or optionally openings, of the infusion lumen, or optionally lumens 4, preferably is from about 2 mm to about 10 mm, more preferably from about 3 mm to about 6 mm, most preferably about 5 mm. As shown in Figure 2A and in Figure 1, in one preferred embodiment of the present invention the various lumens are arranged in a generally parallel manner adjacent to one another. In a second preferred embodiment, depicted in Figures 2B and 2C, the lumens are arranged in a concentric manner, co-axially in a device with two lumens, or optionally tri-axially in a device with three lumens. Shown in Figure 2C is a cross-sectional transverse view along plane 10 in FIG. 2B, in this embodiment, the access lumen 7 is the central lumen with a first infusion lumen 1, and optionally a second infusion lumen 2, arranged around the access lumen 7. Optionally, a device will have two or more infusion lumens with distal openings that feed into a mixing chamber 3, permitting the mixing of two or more components of a hemostatic composition.

The mixing chamber 3 comprises a short-segment chamber at the distal end of the infusion lumens. An opening 4 in the mixing chamber allows mixed materials to exit near the needle tip or distal end of the device, adjacent to the vessel and in close proximity to the vessel puncture site. A more detailed cross-sectional view of the mixing chamber is shown in Figure 3A. Optionally, the mixing chamber has internal baffles or a mesh structure to provide more homogeneous mixing of the hemostatic composition. Optionally, the distal opening of an infusion lumen 4 has blunt edges. Additionally, optionally it is an aspect of the present invention that there be a change in the caliber of the access device between the opening of the access lumen and the opening of any infusion lumen, reducing the risk of accidental insertion of the opening of an infusion lumen into the blood vessel lumen. In a preferred embodiment the device is encased in an outer covering with a generally smooth contour. The proximal opening 6 of an infusion lumen is connected to an infusion device (not shown) from which the hemostatic composition is infused into the desired site. Optionally the infusion lumen terminates with a means 5 of connecting the infusion lumen to an infusion device. An example, which is not intended to limit the scope of the present invention, is a luer lock device, which, optionally, is connected to an infusion device which includes but is not limited to syringes and infusion pumps.

The present invention encompasses a method of employing the device to provide hemostasis during intravascular procedures including but not limited to diagnostic angiography and venography and therapeutic arterial and venous procedures. In this embodiment of the invention, the access device is inserted optionally directly though the skin and though the overlying tissue, into the selected blood vessel such that only the tip of the

device and the distal opening of the access lumen enters the blood vessel. An operator of ordinary skill will recognize when the blood vessel has been puncture by its feel and by the blood return at the proximal end of the access lumen. The operator is prevented from inserting the device sufficiently deep into the blood vessel to allow an infusion lumen into the blood vessel by the change in the caliber of the device between these openings, which substantially increases the resistance to the deeper entry of the device into the blood vessel. Optionally, the location of the opening of the infusion lumen outside the blood vessel lumen is confirmed by aspiration through the infusion lumen to confirm the absence of blood return. Once the blood vessel has been accessed, the hemostatic composition is infused. In a preferred embodiment, optionally a guide wire is inserted through the access lumen into the blood vessel to stabilize the device before the infusion of the hemostatic composition. In contrast to prior methods, because the entry needle remains in place, the hole in the vessel wall is extremely small and is effectively occluded by the needle itself, preventing the delivery of the hemostatic composition into the lumen of the vessel. The hemostatic composition is then injected through the infusion lumen or optionally lumens against, but not into or through the vessel wall and puncture site. Once the hemostatic composition has been placed the planned procedure is performed in the usual manner, with the optional placement of dilators, sheaths, or other such devices. After completion of the procedure the various devices are removed and the vessel puncture site is allowed to seal. The tract in the hemostatic composition through which the various devices are placed is sealed by gentle pressure, optionally elastic recoil of the composition, the flow of the composition into the tract, or the clotting of blood within the tract. Optionally simple digital or other pressure is applied.

The hemostatic composition optionally is thrombogenic, or acts simply as a physical barrier. The present invention permits single- or multi-component liquids, gels, or slurries to be injected near the distal end of the access device, just outside the punctured vessel, while the entry needle is still in place through the vessel wall. Some compositions require multiple components to achieve the proper thickness or firmness. Optionally, multiple infusion lumens are included in this invention for this purpose. Suitable hemostatic compositions include, but are not limited to biological agents including but not limited to fibrin glue/thrombin, calcium or sodium alginate/ionic calcium, collagen paste, and synthetic materials. Additional information about hemostatic compositions is disclosed below. Because these compositions are most frequently in the form of a two part system which, after combination, forms a natural barrier and closure seal, the present invention provides a method for precise mixing of multi-component compositions immediately outside the vessel wall for rapid use in percutaneous vessel closure.

The mixed multi-component composition will harden according to its normal properties immediately outside the vessel and cover the vessel puncture site, effectively closing and sealing the site from further injury or exposure. The sealant material is soft enough to allow passage of a catheter, sheath, and/or vessel dilator that may be placed over a guide wire after removal of the entry needle. At the end of the medical procedure which necessitated vessel puncture, the catheter/sheath is removed and the material remains in place just outside the vessel. Any tract that was created through the material by the catheter/sheath is closed by limited indirect manual pressure, by clotting of blood in the tract, or by elastic recoil of the material to close down to its size at the time of the initial deposition. The

composition material is biocompatible and bioresorbable and can be rendered radio-opaque to allow visualization on fluoroscopy. Over time, the bioresorbable hemostatic composition will dissipate from the closed site, eliminating any requirement for manual removal.

The dimensions for the preferred embodiments of the device include a diameter 21 of up to about 5 millimeters (15 French) for the whole device, more preferably a diameter of about 2 millimeters or less (6 French or less) and lumen diameters of about 1 millimeter (3 French), more preferably of about 0.5 millimeter.

Figure 1 provides a drawing of a cross sectional view of the infusion lumen arrangement in a side by side configuration in one preferred embodiment of the device, to demonstrate a two-part sealant delivery vehicle. The needle lumen is not shown. Components 1 and 2 of the hemostatic composition are provided by tubing coming from individual reservoirs and linked to the infusion lumens by any commercially available hub or connector. The lumens 1 and 2 are connected in a side by side configuration and are linked to the mixing chamber 4 at the distal end 20 and to the reservoirs at the proximal end 30, either in a one piece design as shown or via commercially available needle ports (not shown). Optionally, the mixing chamber 3 is baffled or contains a mesh-like material (not shown) to improve mixing.

Figure 2 shows an example of two component devices whereby the infusion lumens 1 and 2 are attached to the needle lumen 7 in either a side by side configuration (Figure 2A) or a coaxial or tri-axial configuration (Figure 2B). Reservoir connections 5 and tubing 6 are

shown at the top of the device and the reservoirs are not shown but optionally include glass or plastic syringes. The mixing lumen 3 is located near the tip 8 of the needle containing the access lumen 7.

Figure 3A shows an longitudinal cross section of the distal portion of a coaxial embodiment of the present invention. FIG. 3B shows the cross section of the device at level 11 of FIG. 3A. The needle tip 8 and needle or access lumen 7 are shown. Infusion lumen 1 surrounds the needle and infusion lumen 2 surrounds infusion lumen 1. The mixing chamber 3 is shown at the end of the two infusion lumens 1 and 2 and is located near the needle tip 8. Baffles or mesh (not shown) optionally are located in the mixing chamber 3 to increase turbulence and improve mixing of the sealant components.

Another preferred embodiment of the present invention, shown in Figure 4 incorporates a solid hemostatic plug 12 as well a method of using the invention. This embodiment of the invention comprises a solid expansile hemostatic plug 12 , shaped with a slightly blunted distal end 31 to permit positioning against a blood vessel wall puncture site without penetrating the blood vessel wall with the plug. Optionally, the plug has a longitudinally oriented lumen 23 in the approximate center of the plug 12 or at the edge of the plug 12. A needle or other access device 15 passes through the lumen. The plug is surrounded circumferentially by a removable coaxial deployment sheath 13 which optionally provides support, protection and/or lubricity during the placement of the plug. The tip of the deployment sheath 32 is slightly tapered, but is not so tapered that it will allow passage into the artery. The needle 7 or optionally other access device is capable of being used to access a

blood vessel, with the access device tip 8 being inserted within the blood vessel. The deployment sheath 13 is removable and is of a retractable, or optionally of a tear-away design. Exposure of the plug 12 in the deployment location after removal of the deployment sheath 13 permits it to expand and contribute to hemostasis. Optionally, the plug 12 is wetted with a radiopaque or other liquid before insertion.

The present invention includes a method of using this embodiment to provide hemostasis during intravascular procedures including but not limited to diagnostic angiography and venography and therapeutic arterial and venous procedures. In this embodiment of the invention, the access device is inserted optionally directly though the skin and though the overlying tissue, into the selected blood vessel such that only the tip of the device and the distal opening 8 of the access lumen enters the blood vessel. An operator of ordinary skill will recognize when the blood vessel has been puncture by its feel and by the blood return at the proximal end 30 of the access lumen. The operator is prevented from inserting the device sufficiently deep into the blood vessel to force the plug 12 and deployment sheath 13 into the blood vessel by the change in diameter between the tip of the access lumen 8 and the plug 12 with the deployment sheath 13. Once the blood vessel has been accessed, the hemostatic plug 12 is advanced to the desired location against the vessel wall. In a preferred embodiment, optionally a guide wire is inserted through the access lumen into the blood vessel to stabilize the device before the hemostatic plug 12 is moved into position. Because the entry needle 7 remains in place, the hole in the vessel wall is extremely small and is effectively occluded by the needle itself, assisting in preventing hemostatic plug 12 from being forced into the lumen of the vessel. When the hemostatic plug 12 is in the

desired location the deployment sheath 13 is removed optionally by withdrawing it, or if it is of the optional peal away design, by peeling it away. Once the hemostatic plug 12 has been placed the planned procedure is performed in the usual manner. The optional placement of dilators, sheaths, or other such devices is performed by inserting such devices over a guidewire through the hemostatic plug 12. After completion of the procedure the various devices are removed and the vessel puncture site is allowed to seal. The tract 23 in the hemostatic plug 12 through which the various devices are placed is sealed by gentle pressure, optionally elastic recoil of the plug 12, the clotting of blood within the tract 23 or by other means. Optionally simple digital or other pressure is applied.

Another embodiment of the present invention pertains to a solid hemostatic plug 12 as shown in Figure 5 for use after the blood vessel has been accessed, a guidewire inserted, and the insertion device removed. As shown in Figure 5, this embodiment comprises a solid expansile hemostatic plug 12 shaped with a slightly blunted distal 31 end to permit positioning against a blood vessel wall puncture site without penetrating the blood vessel wall with the plug 12. The invention has a channel or lumen 35 through which the guidewire is fed and used to guide the plug 12 to the desired location against the blood vessel wall. Optionally the lumen 35 is formed by a tapered vessel dilator. Preferably, the lumen 35 is formed by a catheter, stent or dilator of a flexible material. The embodiment preferably comprises a stability rod 36, preferably of a plastic material, which aids in directing the plug 12 to the desired location and optionally assists in maintaining it at that location during the removal of the device. The plug 12 is surrounded circumferentially by a removable coaxial deployment sheath 13 which optionally provides support, protection and/or lubricity during the placement

of the plug. The tip 32 of the deployment sheath 13 is slightly tapered, but is not so tapered that it will allow passage into the artery. The deployment sheath 13 is removable and is of a retractable, or optionally of a tear-away design. Exposure of the plug 12 in the deployment location after removal of the deployment sheath 12 permits it to expand and contribute to hemostasis. Optionally, the plug 12 is wetted with a radiopaque or other liquid before insertion. As shown in Figure 6, optionally, the preferred embodiment shown in figure 5 incorporates a longitudinal channel or lumen 16 through which extravascular blood can flow proximally after entering its distal opening 15 when the vessel wall is punctured and blood is extravasated, indicating appropriate positioning of the plug 12 against the vessel wall. The invention is designed to permit the needle 7 or other access device to be withdrawn easily, leaving the plug 12 in position. Optionally, the invention comprises a removal filament (not shown) which is attached to the plug, permitting withdrawal of a malpositioned plug.

The present invention also comprises a method of using this preferred embodiment. This is illustrated in figures 7A to 7G which are provided only for illustration and are not intended to limit the scope to the present invention. In one preferred embodiment the selected blood vessel is accessed with an angiography needle 50. The needle 50 is inserted, optionally directly through the skin 40 and, through overlying tissue, and the tip is inserted through the vessel wall so that the lumen is located within the blood vessel lumen 41. The location of the needle tip within the lumen of the vessel 41 is indicated by a blood return flowing through the access lumen and visible at the proximal end of the needle. Thereafter a guide wire 42 is inserted through the access lumen into the blood vessel lumen as depicted in Figure 7A. The angiography needle 50 is then removed leaving the guidewire 42 in place as shown in Figure

7B. Thereafter, the device is moved into position by feeding the guidewire 42 through the access lumen 7 and advancing the device over the guidewire 42 as shown in Figure 7 C. The device is moved into position but the plug 12 is prevented from entering the vessel lumen 41 by the slightly blunt tip of the plug12 and deployment sheath 13 as depicted in Figure 7D. The deployment sheath 13 is advanced to the measured distance, or until resistance is felt, or optionally until blood is seen to emanate from the device as detailed below. At this time, the deployment sheath 13 (which may be peel-away or retractable) is removed and the plug 12 is deployed and is allowed to expand as depicted in Figure 7E. Optionally the device is then removed leaving the plug 12 and guidewire 42 in place as shown in Figure 7F. Preferably the angiography sheath 51 which comprises part of the device is then advanced into position in the blood vessel 41 as depicted in Figure 7G. The dilator/sheath system 51 used for such vascular procedures preferably is placed by being fed over the guide wire 42 that is inserted through the longitudinal lumen7 that exists in the plug. Optionally, the catheter/sheath 51 may pass adjacent to the plug 12 . At the end of the procedure, the sheath 51 is removed and manual pressure held over the site. The plug 12 is prevented from penetrating the vessel wall by the slightly blunt nature of the distal end of the plug 12.

The material comprising the hemostatic plug is biocompatible and reabsorbable. Immediate additional angiography through the same site is possible if necessary. In a preferred embodiment the material is thrombogenic, relatively soft, and optionally mildly adhesive. Optionally the material is radiopaque due to the addition of radiopaque material including but not limited to barium, iodinated contrast medium, tantalum and tungsten. Suitable materials include but are not limited to collagen fibrin glue/thrombin, calcium or

sodium alginate/ionic calcium, and synthetic materials.

Optionally, the device contains a port for injection down the barrel of the device to allow wetting of the plug with iodinated contrast material prior to deployment or optionally after placement but before removal of the deployment sheath, to allow direct imaging of the plug after deployment.

The devices of the present invention optionally are disposable or re-usable and are preferably made from materials which may be sterilized, including but not limited to metals, plastics or composite materials such as ceramics, or any combination of such materials. A preferred material for use is surgical grade stainless steel for rigid components and surgical grade polyethylene for flexible components. Optionally, Teflon or other protective coatings may be used in areas where there is contact with the hemostatic composition. Optionally the invention is provided to the user packaged in a pre-loaded, pre-sterilized form.

The present invention also comprises the use of alginate derivatives for use as vessel closure materials, as hemostatic compositions, and as hemostatic plugs as defined herein or in other wound closure applications.

Alginate, a biomaterial derived from seaweed, is a polysacharride of d-manuronic acid and 1-guluronic acid that forms a viscous solution when dissolved in 0.9% saline and gels immediately upon contact with divalent cations such as calcium. Alginate derivatives, either liquid or solid, have not previously been used as a material for vessel closure applications.

Alginate is considered an appropriate material for vessel closure because alginate derivatives, specifically calcium alginate supplied as a (solid) woven wound dressing, have been shown to be thrombogenic, nonimmunogenic and bioresorbable. Alginate salts such as calcium alginate or sodium alginate can be produced with varying viscosities. In addition, combining the alginate material with radiopaque materials, thrombogenic materials, and bioadhesives can further enhance its performance as a closure material.

Alginate is most commonly supplied as either sodium alginate or calcium alginate, and may have a preponderance of either the guluronic acid or mannuronic acid derivatives, with higher proportions of guluronic acid providing increased gel strength relative to alginates with a preponderance of mannuronic acid. Also, sodium alginate is soluble in water, however upon increasing the proportion of calcium counterions insoluble alginate salts are generated. The thrombogenicity of alginate is felt to be dependent on the calcium ions that stimulate thrombus formation. Thus, when used as a closure material, the alginate would by necessity contain at least some amount of calcium alginate either alone or in combination with sodium alginate. To achieve the proper viscosity of the material, the proportion of guluronic acid will vary in a range from about 0.1% by weight to about 10% by weight.

The material may be supplied as a single component which would be prepared immediately prior to use, or may be delivered to the outer surface of the vessel wall through a multicomponent delivery system such as is described herein, with the various delivery components carrying 1) the alginate salt, optionally sodium alginate, calcium alginate, or both; 2) a solution containing ionic calcium, to mix with the alginate salt and stimulate

insoluble gels to result in an increased viscosity of the mixed components and for use as a closure material; and optionally 3) radiopaque materials such as barium, iodinated contrast, tantalum, or tungsten; and optionally 4) a bioadhesive and/or a thrombogenic material to enhance overall performance of the material as a closure material. The alginate material is supplied as a liquid of either low or high viscosity, a gel, a foam, or a slurry, while the remaining components (2-4, above) are supplied as liquids. Items under (4) above optionally are directly mixed with the alginate material before addition into the delivery system. The materials listed above (1-4) are infused by multiple infusion devices into multiple infusion lumens of the present invention to deliver the components adjacent to the outside of a vessel wall. Optionally the components are mixed together before being placed into the infusion device and infused through the infusion lumen(s)Optionally the material is used in other devices for other hemostatic applications.

Optionally, bioadhesives and thrombogenic materials are added to the alginate salts to increase rates of healing and closure. In one embodiment of the present invention formulated alginate salts of appropriate viscosity are packaged in pre-sterilized delivery devices, providing surgeons and other physicians with a non-invasive, rapid, bioabsorbable means for closing vascular wounds or punctures. In accordance with one embodiment, a vessel closure material is provided. The material comprises an alginate salt compositions containing varying proportions of the sodium alginate salt, calcium alginate salt, guluronic acid, or mannuronic acid and a medium such as water so as to achieve appropriate physical characteristics of a liquid, gel, slurry, foam, or solid.

Listed below are a series of examples of the present invention. The examples contained herein are intended to illustrate the invention but are not intended to limit the scope of the invention.

Example 1 Coaxial Needle Design for Placement of Injectable Solutions

A device of the present invention was constructed utilizing two different types of arterial entry needles. They are "single-wall" entry needles that have a beveled tip 8 and no inner stylet. Each of these needles are approximately 5 cm length and have a luer-lock hub attached. One needle was approximately 0.052" outer diameter and 0.035" inner diameter 7 (1-part arterial needle, Inrad, Kentwood, MI), while the other was approximately 0.030" outer diameter and 0.018" inner diameter. (Micropuncture introducer needle, Cook, Inc, Bloomington, IN)

Coaxial sheaths were constructed either from modification of commercially-available arterial sheaths. (4 Fr arterial sheath, Cordis Endovascular, Miami Lakes, FL) or from welding of metallic sheaths to the outer portion of the needles. The sheaths used were 4 Fr inner diameter and were cut to a length that, when the needle was placed through the diaphragm of the sheath, the end of the sheath rested approximately 5 mm from the needle tip. The arterial sheath had a side-port attached to its proximal portion that allowed injection of liquids and slurries, and a diaphragm that allowed a water-tight seal around a needle placed through the diaphragm lumen. Subsequently, a smooth, tapered transition from the outer surface of the needle to the outer surface of the sheath was achieved by placing a plastic shrink-wrap tube over the needle-sheath transition and heating the wrap to conform to the

needle-sheath transition. (Heat Shrinking Tubing, Multi-purpose Flexible Polyolefine, 1/16th and 1/8th inch,3M Electric, Austin, TX) Small holes, approximately 1 mm diameter, were cut in the shrink-wrap plastic to allow efflux of the hemostatic composition.

Another prototype design consisted of a metallic outer sheath welded to the outer portion of the needle, with a smooth transition between the outer portion of the needle and the distal portion of the coaxial lumen. A side-port was attached to the proximal portion of the outer lumen to allow injection of liquid materials.

Example 2 Method of Using Invention

Using both canine and swine models, the needle-sheath constructs were placed using percutaneous technique into the common femoral artery, as evidenced by pulsatile blood return through the needle lumen. Guidewires (either 0.035" or 0.018", depending on the prototype design) were placed through the lumen of the needle into the femoral artery. Hemostatic compositions were prepared on the bench. Components have included collagen slurries, collagen slurries mixed with thrombin, avitene mixed with thrombin, fibrin glue mixed with thrombin, and alginate mixed with calcium solutions. In all cases, the materials were rendered radiopaque, ie, visible on X-ray imaging, by addition of approximately 20-30 volume percent of iodinated contrast medium (Omnipaque 300, Nycomed, Princeton, NJ). After placement of the wire and preparation of the material, 3 mL of the hemostatic composition was injected down the lumen. X-ray imaging was performed throughout injection to confirm that the material remained immediately outside the vessel lumen without

penetration into the arterial lumen.

Following injection of the material, the needle apparatus was removed and arterial sheaths and catheters were placed over the indwelling wire, through the hemostatic material, into the arterial lumen. Systemic anticoagulation was achieved with intravenous injection of heparin. Subsequently, the sheaths and catheters were removed and manual pressure applied to the site to achieve hemostasis. Hemostasis was achieved even in the setting of systemic anticoagulation, which is typically impossible without placement of hemostatic devices.

Example 3 Hemostatic Compositions

A variety of hemostatic compositions were made for infusion.

Hemostatic Composition A:

A collagen slurry was made of bovine Type 1 collagen (Bovine type 1 collagen, Collagen Matrix, Inc, Franklin Lakes, NJ), fabricated into an injectable slurry. This was used alone (approximately 3 mL total) or mixed with 10,000 U bovine thrombin (Jones Pharma Inc., St. Louis, MO) dissolved in 2 mL sterile water (equal proportions of collagen and thrombin solution for total of 3 mL).

Hemostatic Composition B:

Avitene (microfibrillar collagen hemostat, MedChem Products, Inc, Woburn, MA) was mixed with sterile water to achieve a viscous solution and mixed with 10,000 U bovine thrombin dissolved in 2 mL sterile water, using equal portions of the avitene and thrombin for a total of 3 mL.

Hemostatic Composition C:

Fibrin glue, obtained from human donors in the usual concentration, (Cathet. Cardiovasc. Diagn. 1997 May;41(1):79-84) was mixed with 10,000 U bovine thrombin dissolved in 2 mL sterile water, using equal portions of the fibrin glue and thrombin solutions, for a total of 3 mL.

Hemostatic Composition D:

1.0% sodium alginate (guluronic acid) (Pronova Biomedical, Oslo, Norway) was mixed with equal volume of 50 mMol calcium chloride, (Fisher Scientific, Fairlawn, NJ) to a total volume of 3 mL of Alginate solution.

Example 4 Hemostatic Plug Device

A 2 mm inner diameter plastic shrink-wrap tube was modified to render one end of the tube smoothly tapered to a diameter of 1 mm by heating with a match and shaving to smooth

taper. A longitudinal slit then was made in the tube. A 2 cm diameter, 30 mm length expandible collagen plug (J. Vasc. Interv. Radiol. 1998 Jul-Aug;9(4):656-9) was loaded into the tube and soaked in iodinated contrast medium (Omnipaque 300, Nycomed, Princeton, NJ). A 19 g arterial entry needle (1-part arterial needle, Inrad, Kentwood, MI) was placed through the collagen plug and out through the tapered end of the tube. The needle was advanced into the femoral artery and a guidewire was placed. The tube was retracted, and its longitudinal slit allowed retraction of the tube with retention of the collagen plug at the

arterial wall. The needle was removed, a sheath placed, and then subsequently removed.

Example 5 Hemostatic Plug for Placement after Access Needle Removal

A 14 F peel-away sheath with a dilator (14 Fr peel-away sheath-dilator, Daig, Minnetonka, MN), was modified for use as a closure device. The dilator was removed, and its distal end was cut to render a blunt surface. A pad of Gelfoam, (Gelfoam absorbable gelatin sponge, Pharmacia and Upjohn Co., Kalamazoo, MI) approximately 2 cm x 2 cm x 0.6 cm was flattened and rolled up to fit into the distal end of the peel-away sheath. After placement of the gelfoam, the cut dilator was placed into the sheath, with the blunt end of the dilator resting along the proximal aspect of the rolled gelfoam pad. Iodinated contrast was injected down the lumen of the dilator to soak into the gelfoam. A needle was placed into the femoral artery of a pig, a 0.035" wire was placed into the artery, the needle was removed, and the sheath/gelfoam/dilator apparatus was loaded onto the wire by passing the proximal end of the wire through the gelfoam and then through the inner lumen of the dilator. The apparatus was passed through the subcutaneous and deeper tissue planes until resistance was encountered, indicating the distal aspect of the device rested on the artery. The peel-away sheath was removed while forward pressure was applied to the dilator, to ensure that the gelfoam would not be pulled superficially during removal of the peel-away sheath. The plug expanded *in situ*, as evidenced by X-ray imaging. The sheath/dilator system was removed, a tapered dilator/sheath was placed over the wire, through the plug, into the artery. The system was then removed, leaving the plug in place, and hemostasis was achieved even in the setting of systemic anticoagulation.

While the preferred forms of the present invention are described and illustrated herein, it will be obvious to those skilled in the art that various changes and modifications may be made therreto without departing from the scope of the present invention . Therefore the descriptions above and the accompanying drawings should be interpreted as being illustrative and not intended to limit the scope of the present invention.

I claim:

1. A vascular access device comprising:

a vascular access needle, said needle having a proximal end and a distal end;

an access lumen within said access needle, said access lumen extending from said proximal end to said distal end of said access needle;

at least a first infusion lumen having a longitudinal axis and a proximal end and a distal end, said distal end opening proximal to said distal end of said access lumen; and,

an infusion device selectively attachable to said proximal end of said infusion lumen, said infusion device being capable of infusing hemostatic material through said infusion lumen to produce hemostasis at a punctured blood vessel.

2. The device of claim 1, further comprising a second infusion lumen having a longitudinal axis and a proximal end and a distal end, said distal end opening proximal to said distal end of said access lumen; and,

an infusion device selectively attachable to said proximal end of said infusion lumen, said infusion device being capable of infusing hemostatic material through said infusion lumen to produce hemostasis at a punctured blood vessel

3. The device of claim 1, wherein said blood vessel is an artery.

4. The device of claim 1, wherein said distal end of said infusion lumen is blunt.

5. The device of claim 1 wherein said access lumen and said first infusion lumen are arranged concentrically.

6. The device of claim 1, wherein said access lumen and said first infusion lumen and said second infusion lumen are arranged concentrically.

7. The device of claim 2 wherein said access lumen is located within said first infusion lumen which is located within said second infusion lumen.

8. The device of claim 1, wherein the longitudinal axis of said access lumen and said infusion lumen are located adjacent and parallel to one another.

9. The device of claim 2, comprising a mixing chamber located near the distal end of said vascular access device, wherein said infusion lumens terminate in said mixing chamber.

10. The device of claim 1 wherein, said infusion device is a syringe provided with manual or mechanical control means for delivery and mixing of a multi-component material.

11. The device of claim 6, wherein said access lumen is located coaxially within said infusion lumen.

12. The device of claim 2, wherein said vascular access needle comprises a second infusion lumen with a proximal end and a distal end, said distal end opening adjacent to said distal end of said first infusion lumen.

13. The device of claim 2, wherein said first and second infusion lumens are located adjacent to one another.

14. The device of claim 2, wherein said first and second infusion lumens are in a coaxial configuration.

15. The device of claim 2, wherein said vascular access device is further provided with a mixing chamber located proximal to said distal opening to said access lumen, said distal opening of said first infusion lumen and said distal opening of said second infusion lumen being connected to said mixing chamber.

16. The device of claim 1, wherein said infusion device is provided with at least one hemostatic composition.

17. The device of claim 1, wherein said infusion device is provided with at least one hemostatic composition selected from the group consisting of calcium alginate/ionic calcium and sodium alginate/ionic calcium.

18. A method of achieving hemostasis during a vascular access procedure comprising the

steps of;

inserting a vascular access device comprising an access lumen with a proximal and distal end, and at least a first infusion lumen with a proximal and distal end, into a blood vessel such that the distal end of said access lumen is located within the lumen of said blood vessel and said distal end of said infusion lumen is located outside said vessel lumen; and,

injecting hemostatic material through said infusion lumen in proximity to said vessel puncture site, for a hemostatic effect.

19. The method of claim 18, further comprising the steps of:

replacing said access device with a device selected from the group of catheters, sheaths and vessel dilators, using a guidewire technique; and

performing a desired vascular procedure.

20. The method of claim 18, wherein the position of said distal end of said access lumen in the blood vessel lumen is confirmed by observing blood return in said proximal end of said access lumen.

21. The method of claim 18, wherein said access device is replaced with a device selected from the group comprising catheter, sheath or vessel dilator, using a guidewire technique; and,

performing a desired vascular procedure.

22. The method of claim 18, wherein at least one component of said hemostatic composition is injected through said first infusion lumen;

wherein at least one component of said hemostatic composition is injected through a second infusion lumen with a proximal and distal end, said distal end being proximal to said distal end of said first infusion lumen;

allowing said components of said hemostatic composition to combine into said hemostatic composition in proximity to said vessel puncture site.

23. The method of claim 18, further comprising the steps of injecting said components of said hemostatic composition through said distal ends of said first and second infusion lumen into a mixing chamber;

allowing said hemostatic components to mix into said hemostatic composition in said mixing chamber; and,

injecting said hemostatic composition in proximity to said vessel puncture site.

24. A vascular hemostatic device comprising:

a hemostatic plug having a longitudinal axis;

a removable deployment sheath having a proximal end and a distal end and a longitudinal axis and surrounding said plug, said deployment sheath having a distal taper;

a channel disposed within said deployment sheath through which a means of guiding said device can pass and along which said plug can be directed to a position adjacent to said blood vessel's wall.

25. The device of claim 24, wherein said deployment sheath is retractable.

26. The device of claim 24, wherein said deployment sheath is adapted to be being peeled away after said access device is used to position said plug.

27. The device of claim 24, wherein said hemostatic device comprises a needle passing through the longitudinal axis of both said deployment sheath and said plug.

28. The device of claim 24, wherein said device has a channel with a proximal and distal end though which extravascular blood emanating from said vessel puncture can flow to the proximal end when the device is disposed adjacent to said vessel puncture site.

29. The device of claim 24, wherein said plug is further provided with a removal filament attached to said plug for use in extraction of a mal-deployed plug.

30. The device of claim 24, wherein said deployment sheath is further provided with an access port whereby said plug can be wetted by the injection of a liquid.

31. The device of claim 30, wherein said liquid is radiographically opaque.

32. The device of claim 24, wherein said infusion device further comprises at least one hemostatic composition selected from the group consisting of fibrin glue/thrombin, calcium alginate/ionic calcium, sodium alginate/ionic calcium, and synthetic

materials.

33. The device of claim 24, wherein said infusion device comprises at least one hemostatic composition selected from the group consisting of calcium alginate/ionic calcium and sodium alginate/ionic calcium.

34. A method of achieving hemostasis as part of a transcutaneous intravascular procedure comprising the steps of:

accessing a blood vessel percutaneously with an access device to create a blood vessel puncture site;

placing a hemostatic plug adjacent to the blood vessel puncture site by moving said plug along the length of the access device until said plug is adjacent to said vessel's surface;

replacing said access device with a device selected from the group consisting of catheters, sheaths and vessel dilators, using a guidewire technique; and,

performing the desired vascular procedure.

35. The method of claim 34, further comprising the steps of surrounding said hemostatic plug with a removable deployment sheath; and

removing said removable deployment sheath said plug is placed adjacent to said vessel wall.

36. The method of claim 34, further comprising the steps of surrounding said hemostatic

plug with a removable deployment sheath; and removing

said removable deployment sheath by peeling said deployment sheath away from said plug after said plug is placed adjacent to said vessel wall.

37. The method of claim 34, further comprising the step of determining the correct location of said hemostatic plug adjacent to said vessel wall by observing the flow of extravascular blood emanating from the vessel wall puncture site along a channel with a proximal and distal end, in the deployment sheath, from said distal end of said channel to said proximal end of said channel which is located above the surface through which said access device is placed.

38. The method of claim 34, wherein said hemostatic plug comprises a removal filament for removal of mal-deployed plug.

39. The method of claim 34, wherein said plug is rendered radio-opaque by wetting said plug with a radio-opaque contrast medium.

40. A hemostatic composition comprising:

a cationic salt;

at least one compound selected from the group consisting of guluronic acid and mannuronic acid; and,

a liquid medium capable of providing said composition with the physical characteristics selected from the group consisting of solid, liquid, gel, and foam.

41. The composition of claim 40 wherein said composition comprises from about 0.5 % by weight to about 5% by weight of guluronic acid.

42. The composition of claim 40 wherein said composition comprises from about 0.5 % by weight to about 5% by weight of mannuronic acid.

43. The composition of claim 40 wherein said cationic solution comprises calcium chloride.

44. The composition of claim 43 wherein said cationic solution contains a concentration of at least about 40 mMol calcium chloride.

45. The composition of claim 40, wherein said composition comprises at least about 0.1% by weight sodium alginate, at least about 0.1% by weight calcium, at least about 1% by weight guluronic acid and at least about 1% by weight mannuronic acid and less than about 98% water.

46. The composition of claim 40 wherein said composition has a viscosity ranging from about 150 to about 300 milliPascals.

47. The composition of claim 40, wherein said composition comprises a radiopaque material.

48. The composition of claim 39, wherein said radiopaque material is selected from the group consisting of barium, iodinated contrast medium, tantalum and tungsten.

49. The composition of claim 39, wherein said radiopaque material is iodinated contrast medium.

50. The composition of claim 40 wherein said composition is selected from the group consisting of a bioadhesive, and thrombogenic material.

51. A method for assisting the closure of a blood vessel puncture site comprising the step of applying a composition comprising a cationic salt;

at least one compound selected from the group consisting of guluronic acid and mannuronic acid; and,

a liquid medium capable of providing said composition with the physical characteristics selected from the group consisting of solid, liquid, gel, and foam.

52. A method for assisting in hemostasis comprising the step of applying a composition comprising a cationic salt;

at least one compound selected from the group consisting of guluronic acid and mannuronic acid; and,

a liquid medium capable of providing said composition with the physical characteristics selected from the group consisting of solid, liquid, gel, and foam.

53. A method for determining the rate of wound closure comprising the step of applying a composition comprising a cationic salt;

at least one compound selected from the group consisting of guluronic acid and mannuronic acid; and,

a liquid medium capable of providing said composition with the physical characteristics selected from the group consisting of solid, liquid, gel, and foam.

54. The device of claim 1 or claim 24, wherein said hemostatic composition comprises:

a cationic salt;

at least one compound selected from the group consisting of guluronic acid and mannuronic acid; and,

a medium capable of providing said composition with the physical characteristics selected from the group consisting of solid, liquid, gel, foam, and solid.

55. The method of claim18 or claim 34 wherein said hemostatic composition comprises:

a cationic salt;

at least one compound selected from the group consisting of guluronic acid and mannuronic acid; and,

a medium capable of providing said composition with the physical characteristics selected from the group consisting of solid, liquid, gel, foam, and solid.

56. The device of claim 16, wherein said hemostatic composition is selected from the group consisting of fibrin glue/thrombin, calcium alginate/ionic calcium, sodium

alginate/ionic calcium, and synthetic materials.

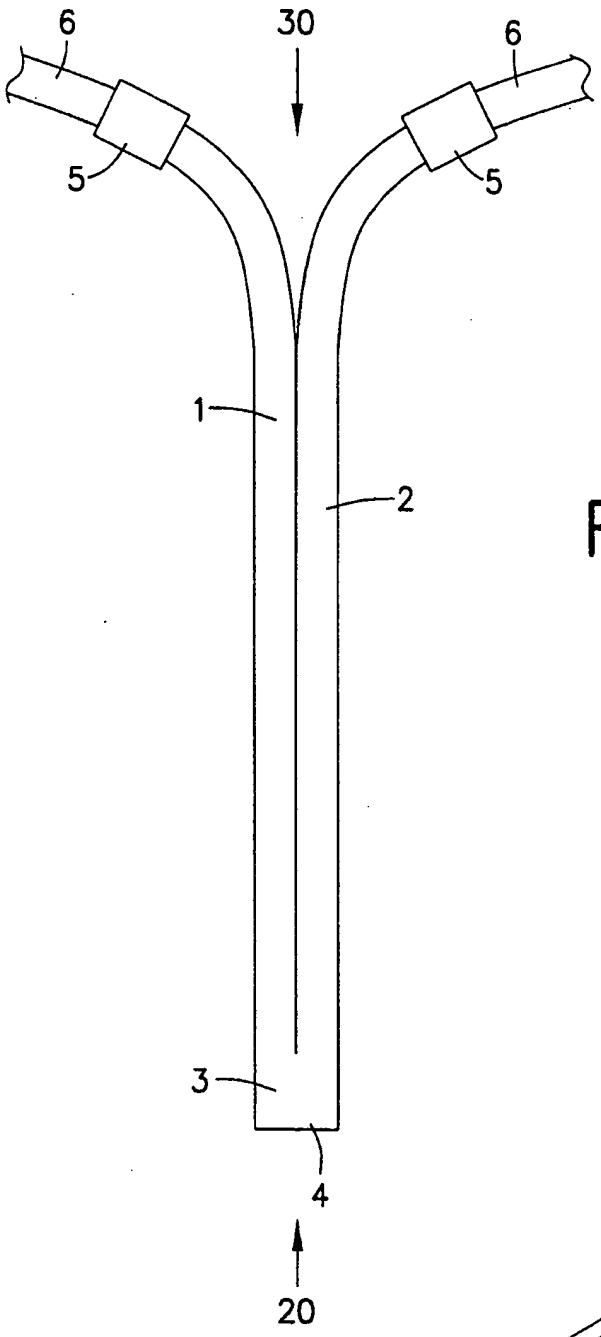


Fig. 1

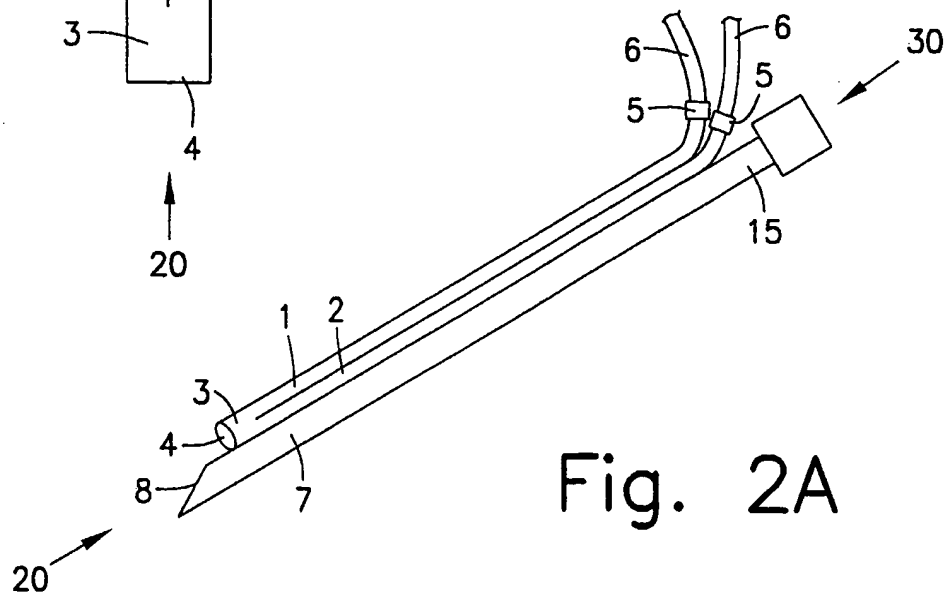


Fig. 2A

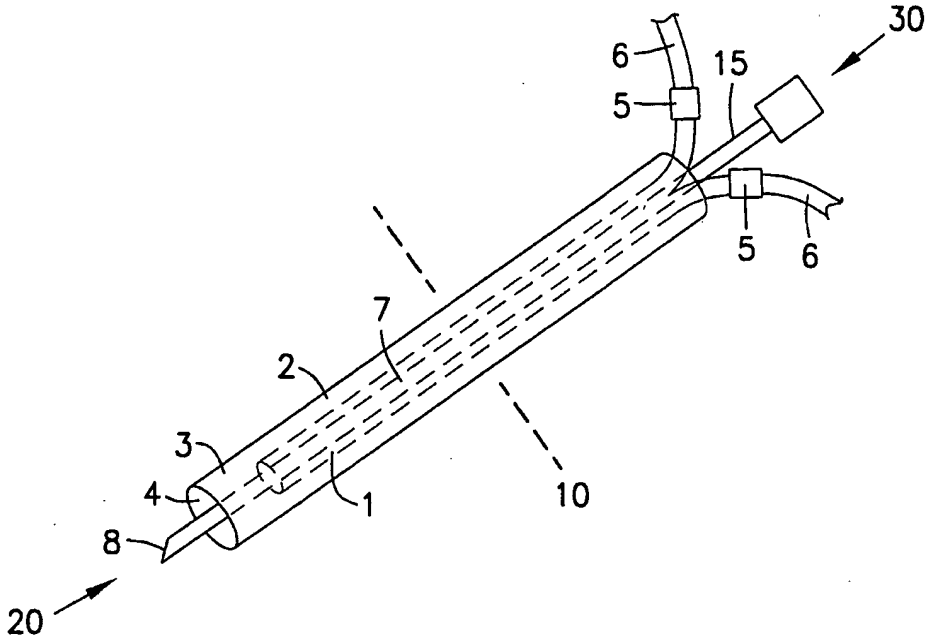


Fig. 2B

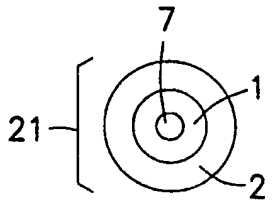


Fig. 2C

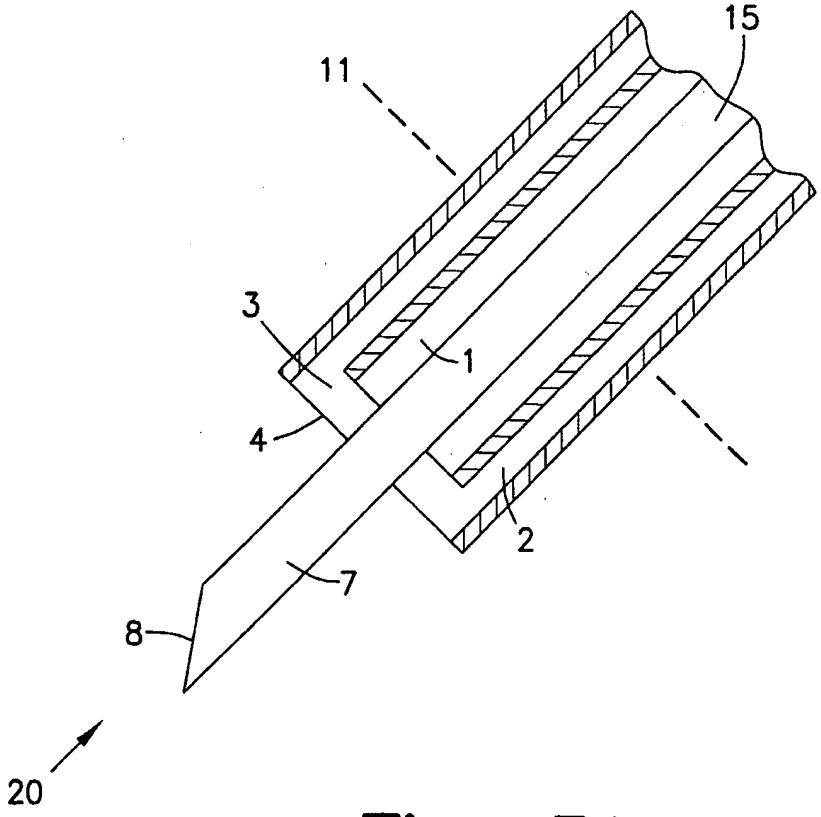


Fig. 3A

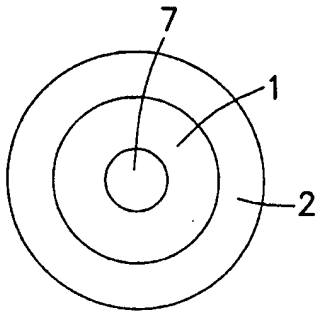


Fig. 3B

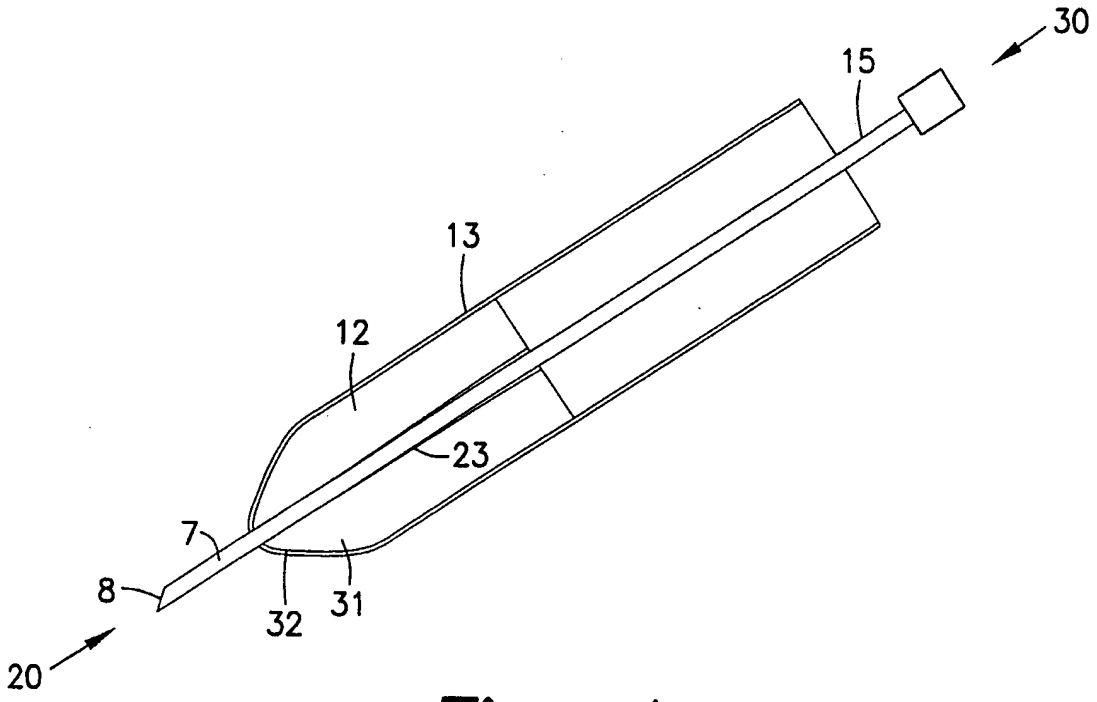


Fig. 4

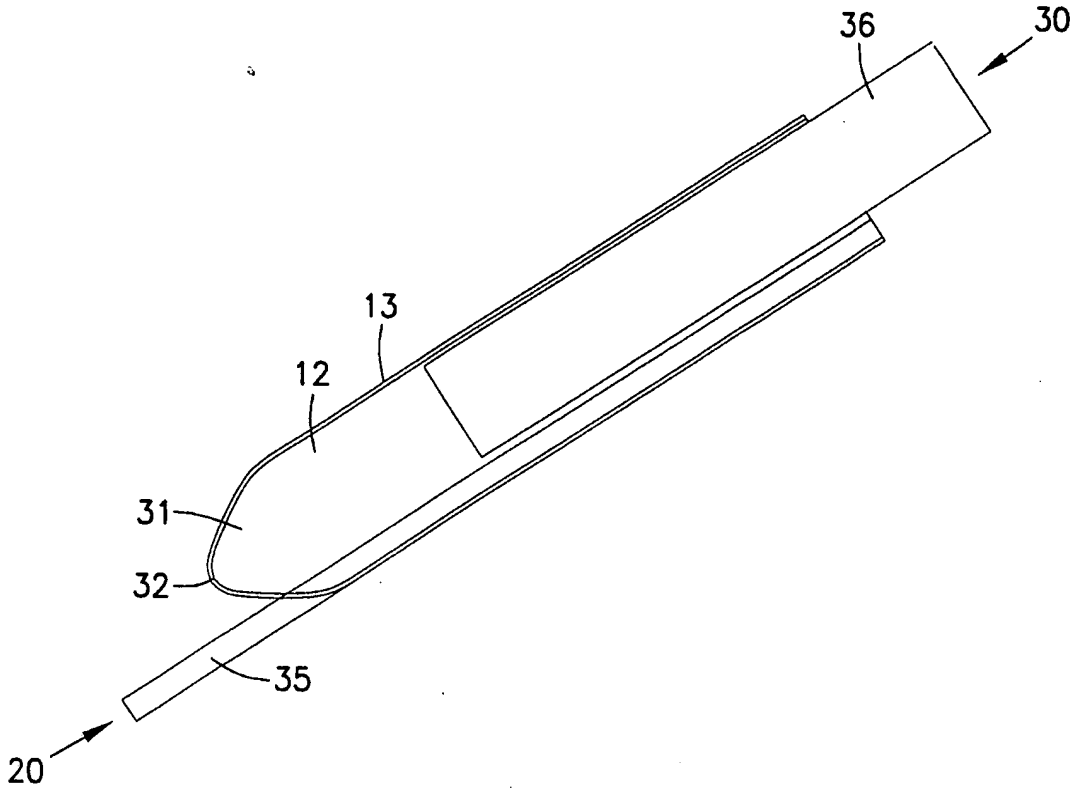


Fig. 5

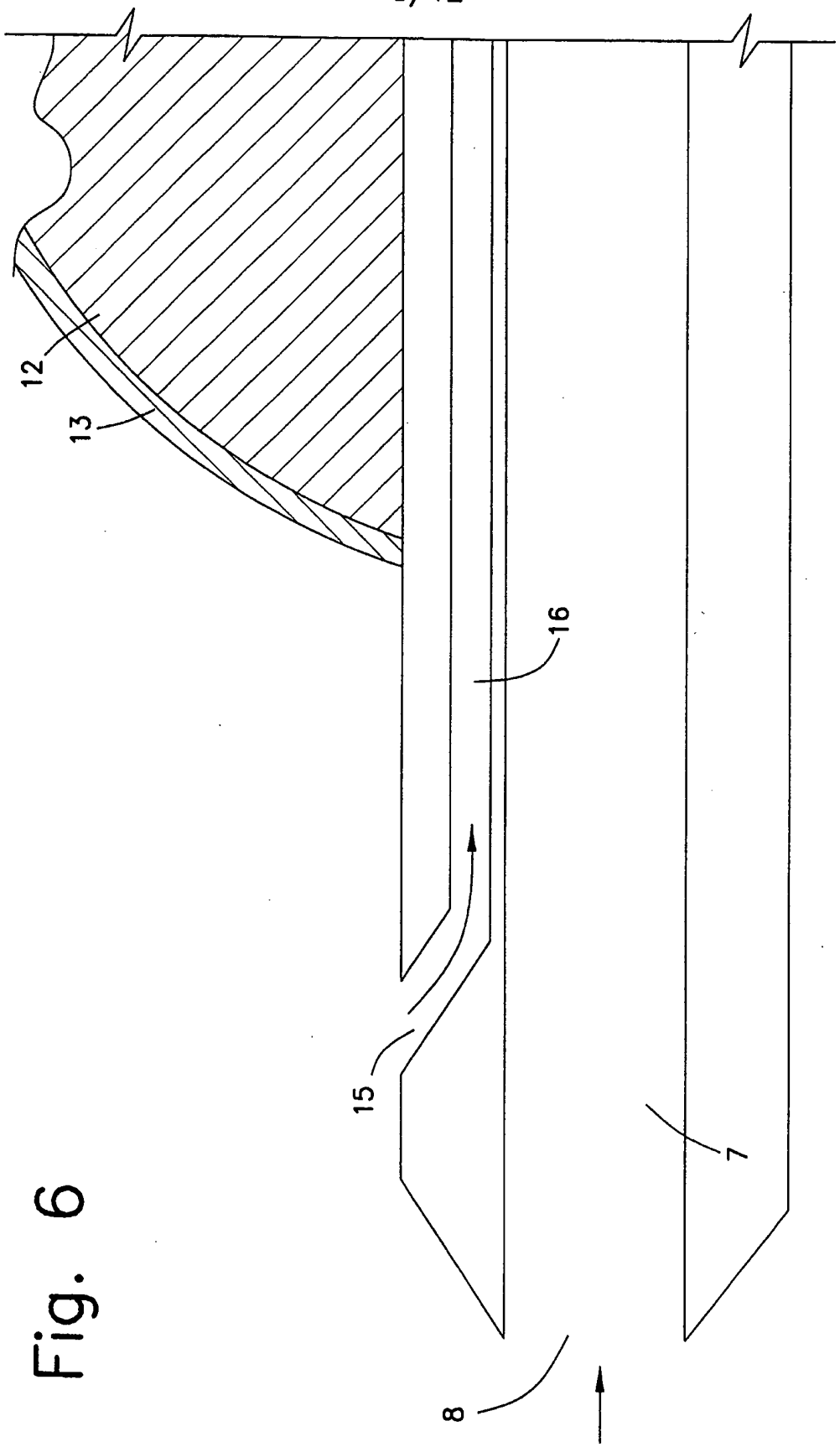


Fig. 6

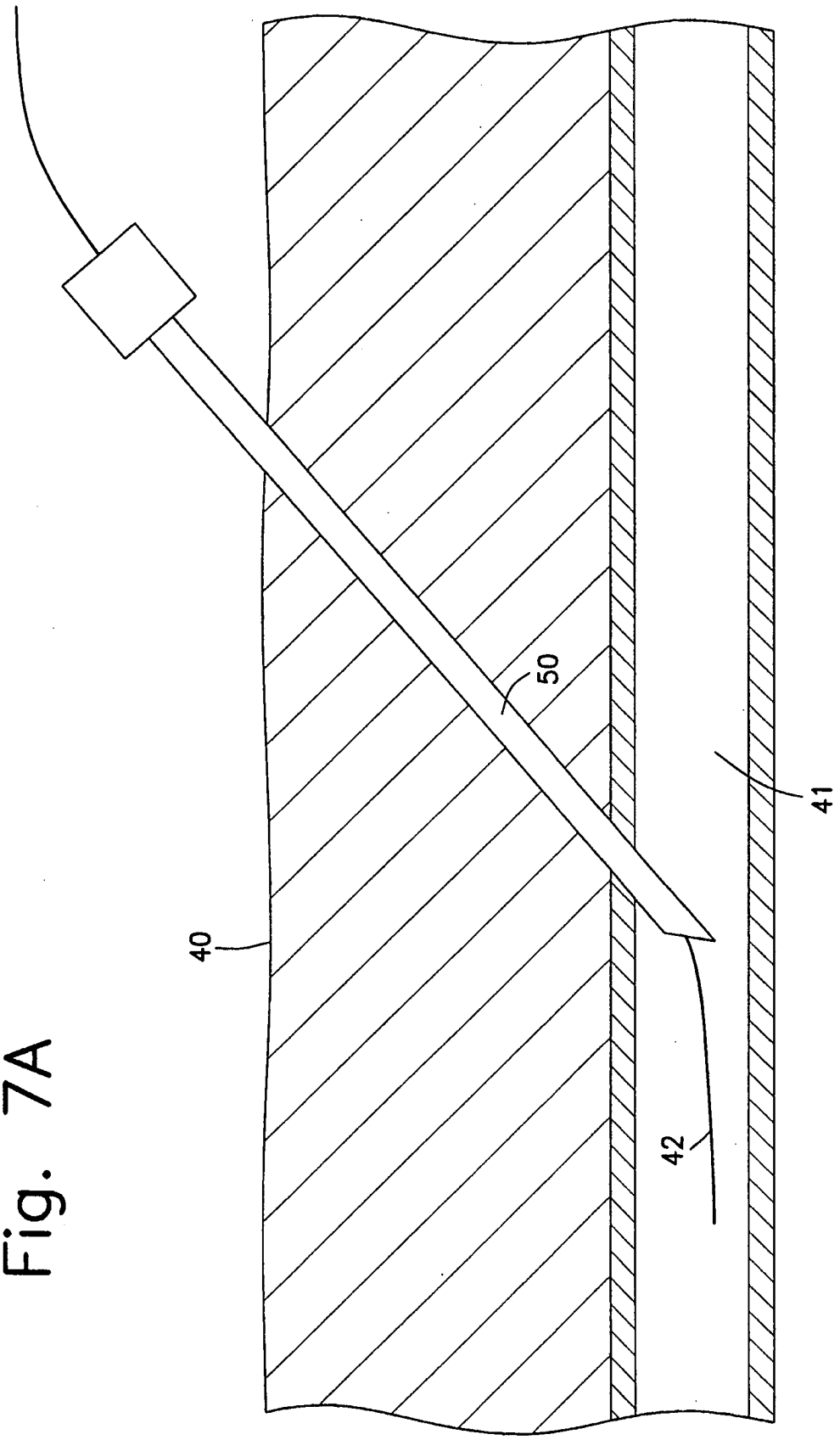
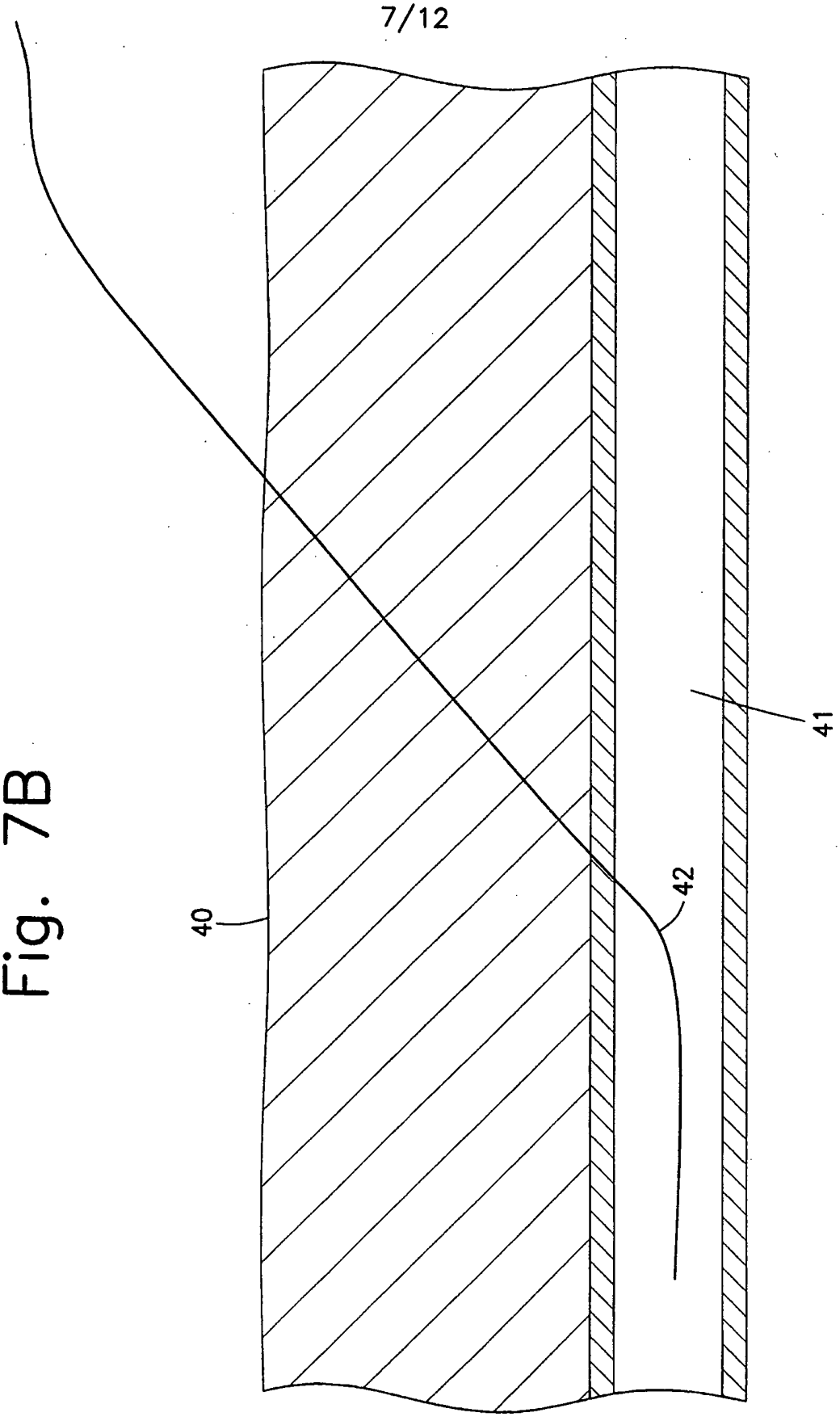


Fig. 7A

Fig. 7B



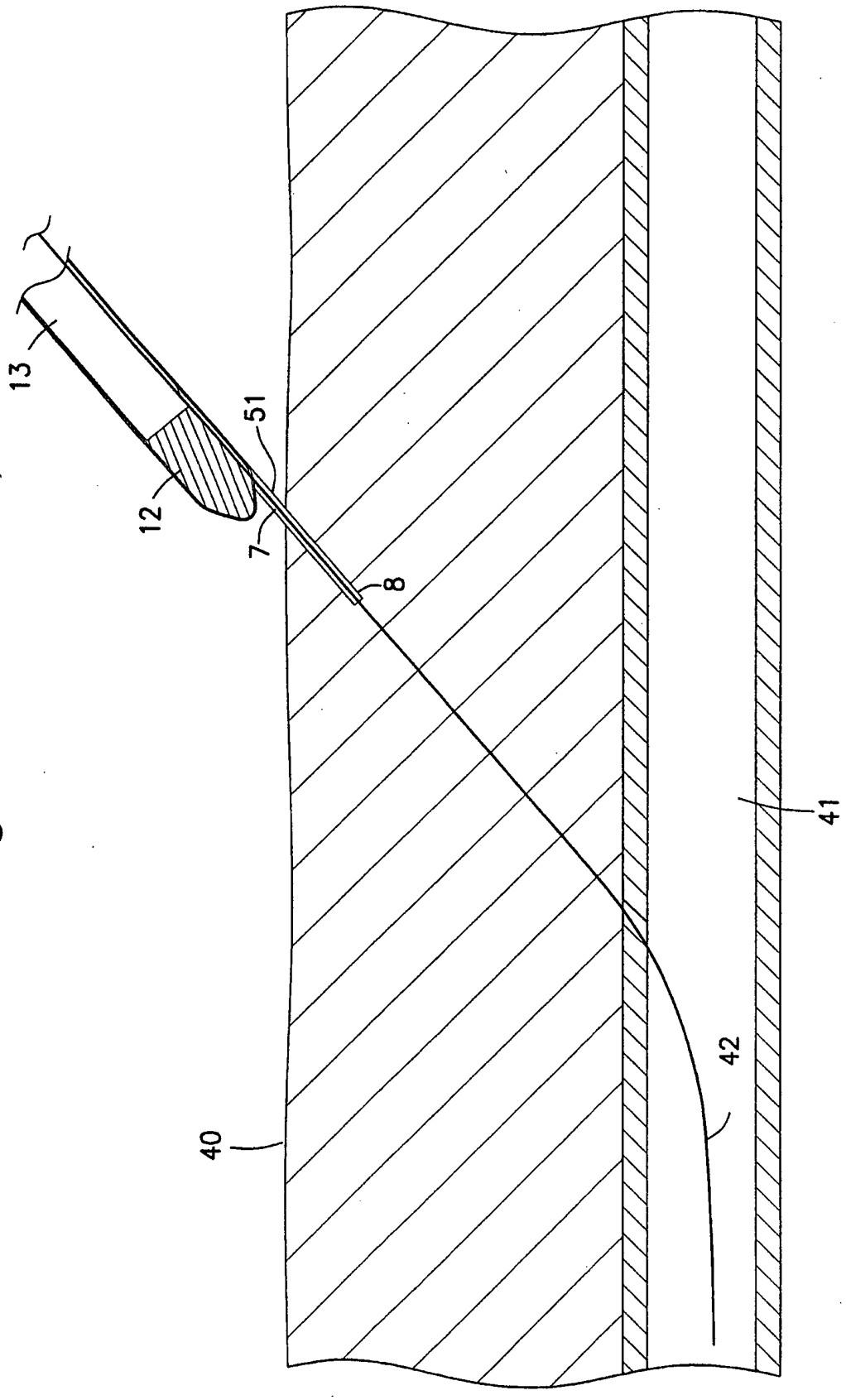


Fig. 7C

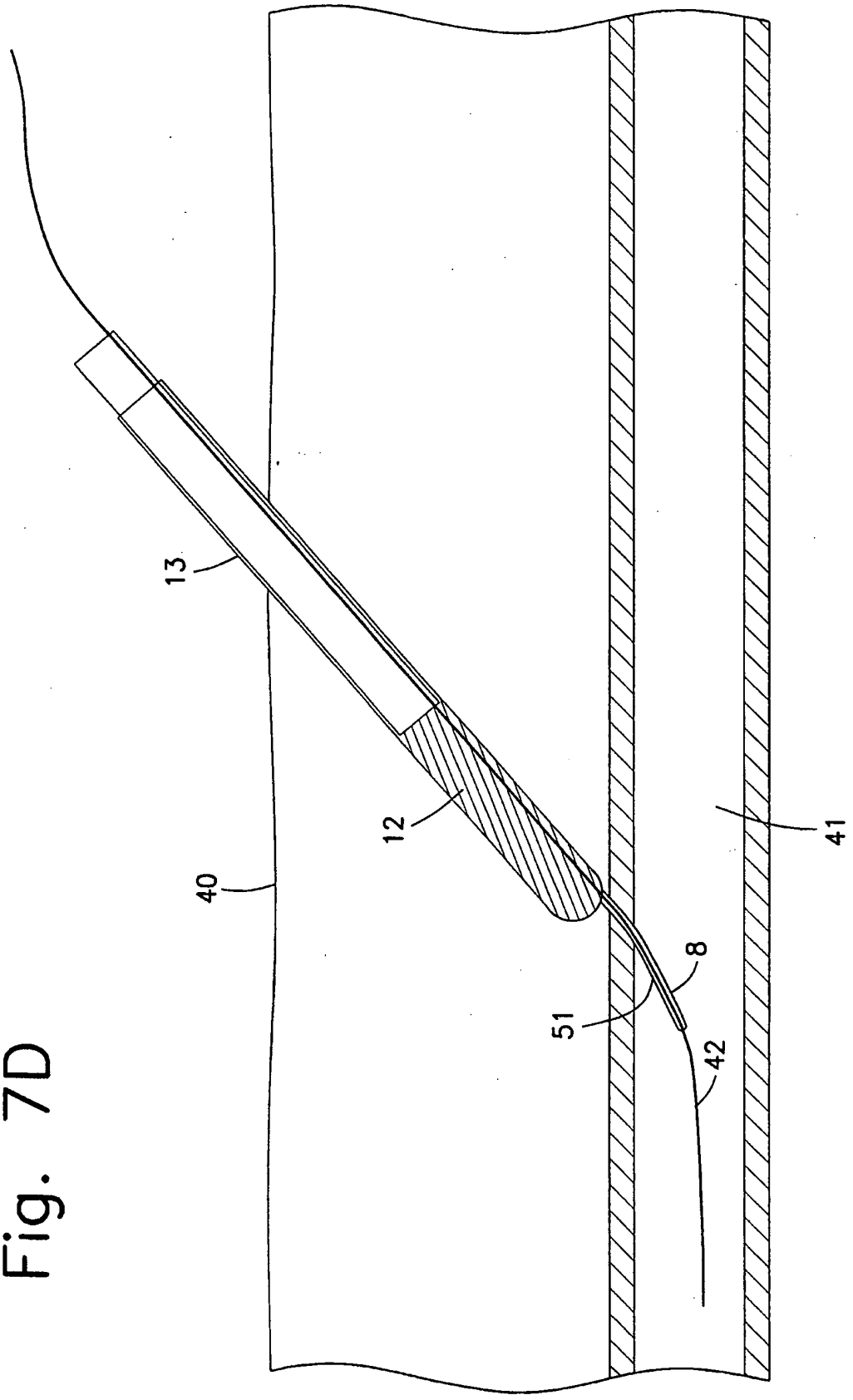


Fig. 7D

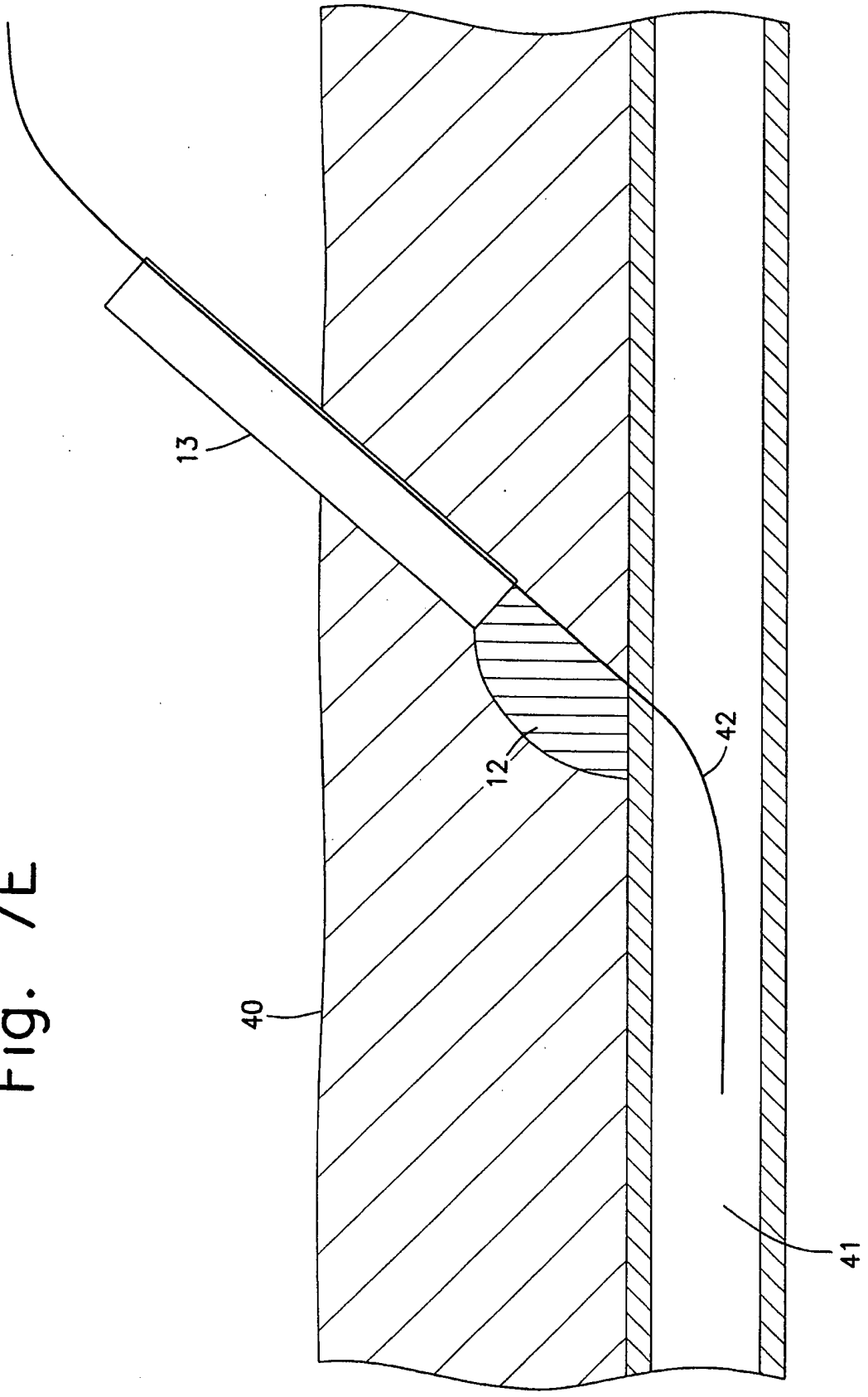


Fig. 7E

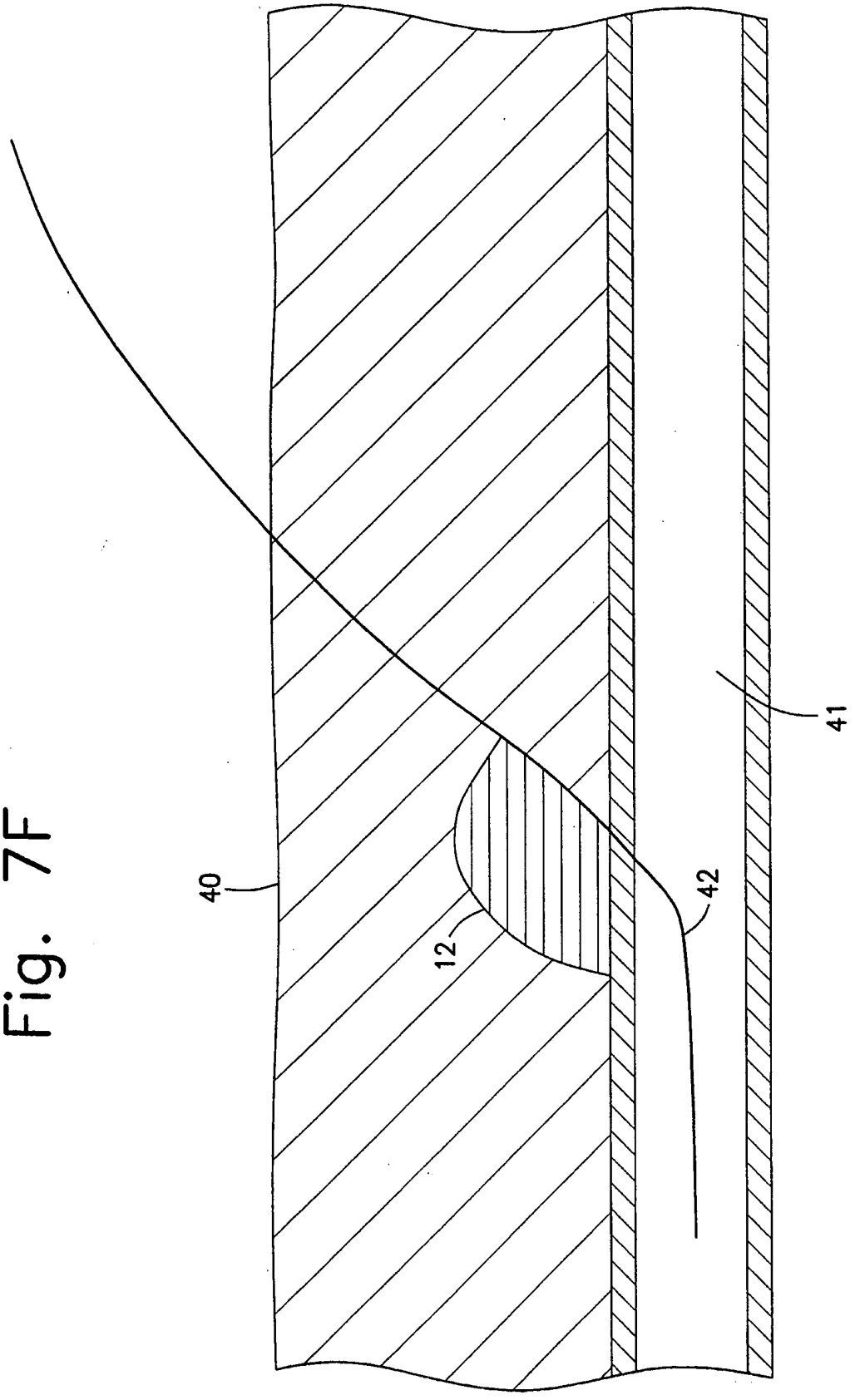
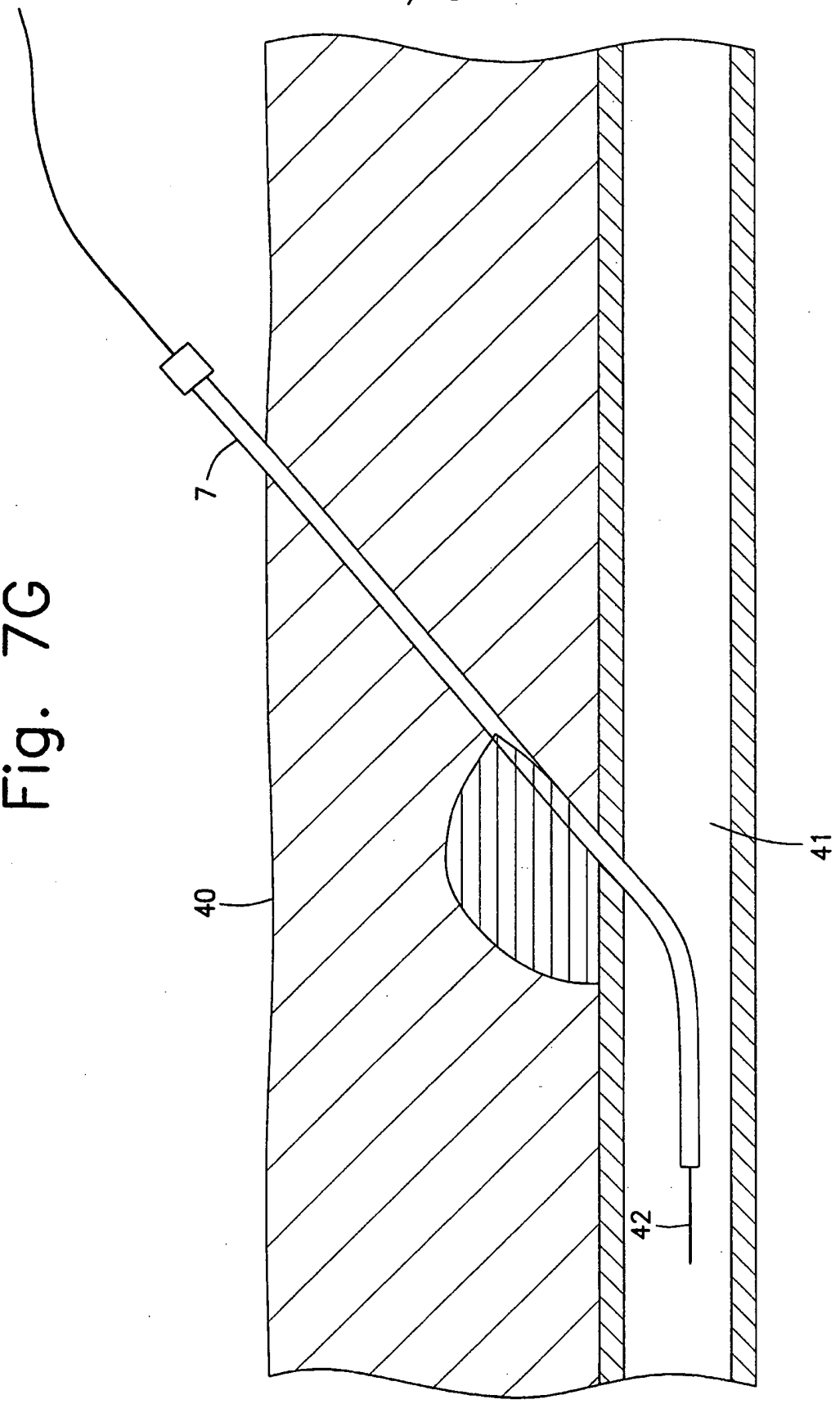


Fig. 7F

Fig. 7G



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/29029

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61B 17/08
US CL :604/506; 606/213

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/11, 57, 60 173, 285, 286, 506-508; 606/213, 214

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,437,631 A (JANZEN) 01 August 1995, Figs. 5-13.	1, 3-5 8, 10, 16, 18-21, 24, 25, 27, 28, 30, 31, 34, 35, 37, 39 --- 17, 32, 33, 36, 51-56

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:	
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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	
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"&" document member of the same patent family	

Date of the actual completion of the international search 15 MARCH 2000	Date of mailing of the international search report 25 APR 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer KELLY M. CHENEY Telephone No. (703) 306-5444

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/29029

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,601,603 A (ILLI) 11 February 1997, Figs 3-5.	1, 3-5, 8, 10, 16, 18-21, 24, 25, 27, 28, 30-32, 34-35, 37, 39, 56 --- 17, 33, 51-55
X	US 5,649,959 A (HANNAM et al.) 22 July 1997, col. 8 lines 48-66, and Figs. 7, 8, 14 and 15.	1-4, 8-10, 12, 13, 15, 16, 18-25, 30-32, 34, 35, 37, 39, 56
X	US 5,486,195 A (MYRS et al.) 23 January 1996, col. 4 lines 6-19, col. 8 lines 12-21, and Figs. 1B, 4, 6B	1-8, 10-14, 16, 18-22, 24, 25, 27, 28, 30-32, 34-35, 37, 39, 56
X	US 5,545,178 A (KENESY et al.) 13 August 1996, Figs. 6 and 7.	24, 25, 29, 34, 35, 38
X	US 5,089,606 A (COLE et al.) 18 February 1992, entire document.	40-50
X	US 5,482,932 A (THOMPSON) 09 January 1996, entire document.	40-50
X,E ----- Y,E	US 6,033,427 A (LEE) 07 March 2000, col. 6 lines 41-66, and Figs. 2, 12	1-4, 8-10, 12, 13, 15, 16, 18-23, 56 --- 17, 33, 51-55
X --- Y	US 5,320,639 A (RUDNICK) 14 June 1994, Figs. 2, 5-9, 12, 13.	24, 25, 27, 28, 30, 31, 34, 35, 37, 39 --- 26, 29, 32, 33, 36, 38, 55

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/29029

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

BRS
Search Terms: alginate, sodium alginate, calcuim alginate, cationic salt, guluronic acid, mannuronic acid, calcuim chloride, hemostatic, hemostasis